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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/761,717	SUN ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *17-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/15/06*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-36 are pending.

Election/Restrictions

The Applicants' election (filed 1/17/06) of Group I, claims 1-16 with traverse is acknowledged. The traversal is on the grounds that restrictions between Groups I and II, I and IV, I and III should be withdrawn since Groups I and II are related as process of making and product, Groups I and IV are both methods of producing an insulinotropic polypeptide which are not considered to be patentably distinct, and similarly, Groups I and III is not patentably distinct process.

The applicants' argument is found to be unpersuasive because the reasons for restrictions between the above-mentioned Groups have been stated in the Office action mailed 11/17/06. The Office action has set forth that "where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04".

Further, the response discusses the addition election with regard to Group IV, and submits that examining all the peptide sequences (SEQ ID NOs:1-2 and 4-18) would not be a serious burden to examine all of the claims together.

The applicants' argument is not persuasive because said peptide sequences are directed to polypeptide variants comprising single or double substitution mutations; searching for all of the sequences containing the mutations is a serious burden to Examiner.

Thus, the requirement is still deemed proper and is therefore made FINAL.

Claims 17-36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Therefore, claims 1-16 are under examination to the extent that they are drawn to the elected invention.

Priority

On page 2 of the declaration filed 4/2/04 state that applicants do not claim priority. However, contrary to this, the specification set forth that this application claims the priority to Chinese Patent application No. 01126278.8 filed 7/19/2001. Clarification in this regard is required.

Applicant is advised of possible benefits under 35 U.S.C. 119(a)-(d), wherein an application for patent filed in the United States may be entitled to the benefit of the filing date of a prior application filed in a foreign country.

Specification/Claim/Objections

The disclosure is objected to because of the following informalities:

On paragraph [0025-0026], the descriptions to Figures 2 and 3 do not set forth the sequence identifiers (SEQ ID NOs:_) for the amino acid sequences set forth in Figures 2 and 3.

In paragraph [00129], line 4, "MWCO" should be spelled out for the first instance of use.

In claim 1, item b, "combination genes..." should be changed to "combination of genes ..."; and item d", "expressing into" should be changed to "expressing in".

In claim 3, "Xhol I" should be changed to "XhoI".

In claim 16, "Clostrispan or Trypsin" should be changed to "clostrispan or trypsin".

Appropriate correction is required.

IDS

The references cited in the IDS filed 3/15/06 have been considered by the examiner.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, item *a*, recites "*may encode the GLP-1(7-36) polypeptide ....*" which is conditional language; it is not apparent whether or not action of the encoding actually occurs. Similarly, see also claims 9-10.

Claim 1 is indefinite because the claim item *b*, is directed to ligation at least two nucleotide sequences comprising cohesive restriction sites at each ends of the said sequences, whereas item *b* also sets for the limitation "wherein N is integer from **1** to 32" in which N is integer 1 does not conform with said ligation.

Claim 1, item *b*, recites "*vector N copies of ...*" appears to be awkward and unclear because it may refer to the vector that contains N copies of the polynucleotide encoding the GLP-1(7-36) polypeptide, or N copies of said vector. The claim should make it clear in this regard. Provided that the vector refers to the vector already has the N copies of said gene, the claim is vague as to whether or not cloning of the ligation product which comprises tandem repeat of the GLP-197-36) polynucleotides in to said vector is carried out; this would result in the copy number larger than "N" as claimed of the polynucleotides in said vector.

The recitation of claim 1, item *b*, "*...combination .... or...*" is indefinite because the term "or" is improperly used here. Also, claim 1, item *b* (step b), recites "*wherein N is an integer from 1 to 32*" whereas item *d* which is the subsequent step of said step b recites "N copies" (plural form), i.e., multiple copies of N; thus, the recitation of item *b* ("N is an integer 1") is inconsistent with the recitation of item *d* ("N copies") thereof.

Claim 1, item *d*, recitation "*a fusion protein*" is unclear because it ambiguously refers to (i) fusion of GLP-1(7-36) polypeptide with a heterologous amino acid sequence(s), or/and (ii) fusion between the genes encoding GLP-1(7-36) polypeptide.

Further, claim 1, item *e*, recites "*cleaving the fusion protein*"; the claim does not make it clear that (i) whether or not said cleavage is random or a sequence-specific which is fundamental important to the claimed invention; (ii) the cleavage occurs *in vivo* (e.g., the cleavage takes place inside the host cell expressing the fusion protein) or *in vitro* (e.g., the cleavage takes place after breaking down he host cell and before step *f*).

Claims dependent from claim 1 are also rejected.

Claim 16 recitation "... *claim 1 wherein said protease* ..." has no antecedent basis in claim 1 from which claim 16 depends.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Deposit requirement

Claims 1-16 are rejected to because claims 8 and 15 recite that the vector set forth in instant claim 1 is deposited at "China Committee for Culture Collection of Microorganism General Microbiological Culture Center" under accession number "CGNCC No. 0559" (a bacterial strain (see paragraph [0074]) comprising said vector. Since the vector comprising the a number of tandem copies of the gene encoding the GLP-1(7-36) polypeptide or/and analog thereof are essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the organism is not so obtainable or available, the requirement of U.S.C. 112 may be satisfied by a deposit of the microorganism.

The specification is objected to because of "CGNCC No. 0559" (see paragraphs [0069] and [0074] and page 40) for the same reasons stated above and below.

The applicants have apparently incorporated specific references into the specification does not eliminate the issue of public availability and permanence as the strain cited in the references and the reference *per se* do not indicate public availability of the starting materials inasmuch as the biological materials motioned in a publication may be proprietary and not publicly available.

The specification does not disclose a repeatable process to obtain the microorganism from which the vector is to have been obtained nor is it apparent that the host cell having accession No. "CGNCC No. 0559" is readily available to the public. It is noted that the applicants have deposited the microorganism but there is no indication in the specification as to public availability. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strains have been deposited under the Budapest Treaty and that the strain

will be irrevocably and without restriction or condition releases to the public upon the issuance of a patent and receipt showing the appropriate biological material was received and entered into the depository, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809 applicants may provide assurance of compliance by an affidavit or declaration, or by statement by an attorney of record over his or her signature and registration number indicating that:

a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

b) all restriction upon availability to the public will be irrevocably removed upon granting of the patent;

c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

d) a test of the viability of the biological material at the time the deposit was made and that such test result indicated that said biological material was viable (see 37 C.F.R. 1.807); and

e) the deposit will be replaced if it should ever become unviable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note that the following rejection is based on that claim 1 (items *a* and *b*) as written read on that ligation of the nucleotide sequence comprising tandem repeat cDNA sequences encoding GLP-1(7-36) polypeptide into a vector, wherein the step a of introducing appropriate restriction sites can be done by PCR reaction.

Claims 1, 4-5, 9-10, 13 and 16 are rejected under 35 U.S.C. 102 (e) as anticipated by Rasmussen et al. (WO 9517510).

In the patent claim 1 and Examples 1-7, Rasmussen et al. teach a method of recombinant production of a tandem repeat GLP-1 polypeptide comprising multiple copies of GLP-1(7-36) polypeptide, wherein the polynucleotide encoding the tandem repeat GLP-1 (named the GLP-1 cassette) was digested with restriction enzymes BamHI and XbaI and subcloned into a cloning vector pSKII+ (see Example 1 at pages 9-10); then, the cassette was subcloned as a BamHI-XbaI fragment into the BamHI-SpeI sites of an expression vector, pET3a (see Example 12 at page 12) wherein said cassette comprises four copied of GLP-1(-36) cDNA sequences. The resultant expression vector is transformed into a host cell, e.g., *E.coli.* strain MC1061 (Example 3 at page 15). Also, Rasmussen et al. teach recovering the resulting tandem repeat GLP-1 polypeptide from the bacterial culture (claim 1, item d) and digesting said polypeptide with protease trypsin (see Examples 6 and 7 at pages 18-19) followed by isolating/purifying the trypsin-digested product which is GLP-1(7-36) monomer polypeptide (see Example 4 at page 17, line 16) using HLPC chromatography (see Example 4, page 16, lines14-16, and Example 6, page 18, lines 22-24). Thus, Rasmussen et al. teach the method of claim 1 as set forth above.

The copies of GLP-1(7-36) is four, which meets the limitation of instant claim 4.

On page 5, lines 12-14, Rasmussen et al. teach that the cassette can contain more that six copies of gene encoding GLP-1(7-37), which anticipates instant claims 5 and 9-10 .

Since in the above-discussed method, the host cell is *E.coli.*, the above Rasmussen et al. teachings anticipate instant claim 13.

In the above-discussed method, the protease used to cleave the tandem repeat GLP-1 ("precursor") is trypsin, which anticipates instant claim 16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 9-10, 13 and 16 are rejected under 35 U.S.C. 102 (e) as obvious over Rasmussen et al. (WO 9517510).

In the patent claim 1 and Examples 1-7, Rasmussen et al. teach a method of recombinant production of GLP-1(7-36) comprising:

(i) generating a cassette (a nucleotide sequence) comprising tandem-linked four GLP-1(7-36) coding units, e.g., four copies of cDNA sequence encoding GLP-1(7-36) polypeptide; wherein generating the cassette is accomplished by ligation between two or more said cDNA sequences (see page 4, the last paragraph); this step is equivalent to the instant claim 1 steps (a) and (b) in light of that step (a) of introducing a cohesive ends in the DNA sequences for the subsequent ligation has been inherently taught by "Sambrook et al. "*Molecular Cloning – A laboratory Manual*" (*a reference incorporated, see page 5, lines 1-2*) which is the well-known and routinely used manual book for molecular cloning;

(ii) transforming the expression vector (see Example 1) comprising said cassette into a host cell, e.g., *E.coli.* (see Example 3); (iii) expressing the four tandem-repeat GLP-1(7-36) polypeptide in said host cell (see Example 2); (iv) converting GLP-1 "precursor" (e.g., a tandem tetramer) that comprises the four tandem-repeat GLP-1(7-36) polypeptides to active GLP-1(7-36) monomer by digestion (cleavage) with protease trypsin (see Examples 6 and 7); and (v) isolating/purifying the trypsin-digest product (see page 17, line 16) using HLPC chromatography (see Example 4, page 16, lines14-16, and Example 6, page 18, lines 22-24). The above Rasmussen et al. teachings meet the limitation of instant claims 1 and 4.

On page 5, lines 3-11, Rasmussen et al. teach that the DNA construct produced by the ligation of two or more DNA sequences encoding GLP-1(7-36) which is done by established standard method. It is art recognized that hundreds of restriction enzymes useful for DNA and some of them are exchangeable (see pages 4-5 and 10-12). It would have thus been obvious to one skilled in the art to recognize and use restriction enzymes including BglII, BamHI, Sal I or and XhoI. The above Rasmussen's teachings are therefore applicable to instant claims 2-3.

On page 5, lines 12-14, Rasmussen et al. teach that the cassette can contain more that six copies of gene encoding GLP-1(7-37), as applied to instant claims 5 and 9-10 .

Since in the above-discussed method, the host cell is *E.coli.*, the Rasmussen et al. teachings is applied to instant claim 13.

Since in the above-discussed method, the protease used to cleave the GLP-1 "precursor" is trypsin, the Rasmussen et al. teaching is applied to instant claim 16.

Rasmussen et al. do not provide working example(s) or disclose in the their patent claims that the cassette is accomplished by ligation of nucleotide sequences encoding GLP-1(6-7-36). between two or more said cDNA sequences.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop the method of producing bioactive GLP-1(7-36) peptide by molecular cloning according to the above-discussed approach, wherein the cassette nucleotide sequence encoding the tandem repeat GLP-1(7-36) polypeptide is constructed by the above mentioned ligation process. One skilled in the art would have been motivated to do this because Rasmussen et al. have clearly taught that the cassette can be made by ligating two or more said

cDNA sequences encoding GLP-1(7-36) (see page 4, the last paragraph). Thus, one skilled in the art would have constructed the cassette according to the Rasmussen's teaching and according to the well-known Sambrook et al. "*Molecular Cloning – A laboratory Manual*" (a reference incorporate, see page 5, lines 1-2, of Rasmussen et al.).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4-16 are rejected under 35 U.S.C. 103(a) as obvious over Rasmussen et al. (WO 9517510), taken with Xia, Y. (US 2002/0081735 A1).

The rejection to instant claims 1, 4-5, 9-10, 13 and 16 has been discussed above.

Rasmussen et al. do not expressly teach in their method that the copy number in the cassette that encodes multiple copies of cDNA encoding GLP-1(7-36), and that the host cell is HB101, JM103, JM109, DH5α, or C600, or bacterial strain having deposit No. 0599.

Rasmussen et al. have taught the above-mentioned cassettes can comprise more than six copies of the cDNA sequences thereof (see page 5, lines 12-14). Hence, the skilled artisan would have chosen high number including the copy number 16 or 32 to construct the cassette for producing the GLP-1 precursor which comprises high copy number (e.g., 16 or 32) of GLP-1(7-36) polypeptide. The Rasmussen et al. teaching is applied to instant claims 6-7 and 11-12.

Xia teaches that bacterial strain, e.g., HB101 or JM109 is suitable for expressing bioactive GLP-1 peptide (see the patent claims 9, **12**-16), as applied to instant claims 8, 14 and 15.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop the method of genetic-engineeringly production of bioactive GLP-1(7-36) polypeptide by enzymatic cleavage of the GLP-1 precursor molecule which comprises tandem-repeat multiple copies (e.g., 16 or 32) of GLP-1(7-36) polypeptide thereof, wherein the host cell used to express the GLP-1 precursor is a bacterial strain, e.g., HB101. The bacterial strain having deposit No. 0599 is also included in the rejection because said strain is an *E.coli.* strain (see instant claims 14-15 which is within ordinary knowledge and skills of the skilled artisan during transformation of said strain with the above-mentioned expression vector. One skilled in the art would have been therefore motivated to do this because of the following reasons.

(i) Rasmussen et al. have taught that their DNA construct is suitable for more than tow or more than six (tandem repeat) cDNA sequences encoding GLP-1(7-36) polypeptides (see page 4, lines 24-27, and page 5, lines 12-13).

(ii) Rasmussen et al. have demonstrate high yields of production of the GLP-1 precursor comprising multiple copies of GLP-1(7-36) gene in the transformed bacterial host cells (see page 3, lines 24-26). Hence, one skilled in the art would have readily cloned the above-discussed cassette containing copy number (e.g., 16 or 32) of the tandem-repeat cDNA sequences encoding the GLP-1(7-36) polypeptides, expressed the GLP-1 precursor in the bacterial host cell, e.g., HB101 as taught by Xia in high yield, and isolated/purified the bioactive GLP-1(7-36) monomer polypeptide after cleavage of the GLP-1 precursor.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

The following art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

• Selden et al. (US 5994127) teach expression of GLP-1(7-37) polypeptide, an analog of instant GLP-1(7-36), in a mammalian cell, wherein the GLP-1(7-37) polypeptide is fused to s signal peptide (Example 11). Yet, Selden does not teach or suggest nucleotide sequence comprising multiple copies (at least two) of the gene encoding GLP-1(7-37) and expression polypeptide encoded by the nucleotide sequence thereof. Thus, the Selden et al. patent is not a prior art.

• Xia Y. et al. (US6316224 B1) teach production of GLP-1(7-36) polypeptide by expressing plasmid (Figure 5) comprising polynucleotide encoding multiple copies, e.g., 3 or 8 copies of GLP-1(7-36) (see Example 11). However, Xia et al. does not teach or suggest that construction of said polynucleotide via the ligation approach of molecular cloning, and that the produced polypeptide containing the multiple copied of monomer GLP-1(7-36) is subjected to enzymatic (protease) cleavage followed by isolation/purification of the monomer GLP-1(7-36) polypeptide. Hence, Xia's patent is not a prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.
July 12, 2006

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER